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Therapies for rheumatoid arthritis: hope springs eternal

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Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease, the pathology of which is primarily and symmetrically localized in diarthrodial joints. At the time of writing, ~1% of the world's population was suffering from RA. The pathogenesis of RA is characterized by an inflamed synovium (lining the joint cavity), degradation of articular cartilage and erosion of subchondral bone. The systemic ramifications of this disease, with their attendant morbidity and mortality, include cardiopathy, nephropathy, vasculopathy and pulmonary and cutaneous disorders. Although the cause of RA is unknown, the presentation of an arthritogenic self-antigen to a genetically susceptible individual is believed to trigger the activation of autoimmunological pathways that lead to RA [1]. Intense investigation of the cause of RA has uncovered many of the integral biochemical, cellular and molecular pathological components and pathways of this disease, leading to the discovery, development and marketing of new and novel therapeutics that target several seminal components of RA. This article provides an assessment of the 'state of the state' of RA therapy and offers perspectives on what hope the future might afford victims of this disease.

Inflammation, anti-inflammatories, analgesics and the cyclooxygenase-2 conundrum

Inflammation constitutes an integral component of the pathogenesis of joint disease in RA patients. Indeed, the periodic flare-ups observed in arthritic joints manifest the clinical signs and symptoms of inflammation [2]. Aspirin and nonsteroidal anti-inflammatory drugs, NSAIDs, (e.g. motrin, diclofenac, naprosyn) have, for many years, been a front-line therapy for treating the pain and inflammation of RA. An unfortunate consequence of NSAID therapy, however, is the common occurrence of gastrointestinal irritation. Although analgesics (e.g. acetaminophen, oxycodone) are free of this gastrointestinal liability, and do relieve RA-associated pain, they do not affect joint inflammation. However, in selected situations physicians treat RA patients with a combination of an NSAID and a gastroprotectant, such as a proton pump inhibitor, histamine receptor antagonist or misoprostol [3]. Accordingly, efficacy for pain and inflammation, achieved with a drug formulation such as Arthrotec® (diclofenac in combination with misoprostol, Pharmacia and Searle) [4], in the absence of little or no gastrointestinal side effects has frequently been achieved with these therapeutic regimens.

The pharmaceutical industry has endeavored to discover, develop and market an efficacious NSAID with little or no gastrointestinal liabilities. This has led to the arrival of the cyclooxygenase (COX)-2 inhibitors, a new class of NSAID that is prominently represented by Vioxx® (Rofecoxib, Merck), Celebrex® (Celecoxib, Pfizer) and Bextra® (Valdecoxib, Pfizer). Although these drugs demonstrate analgesic and anti-inflammatory activity comparable with traditional NSAIDs, they cause markedly less gastroduodenal irritation than aspirin and the traditional NSAIDs [5]. Mission accomplished, or maybe not! Imagine the disbelief, anxiety and frustration experienced by RA patients when Merck voluntarily withdrew Vioxx® from the market in 2004 because it was demonstrated to increase the risk of heart attacks and stroke in some individuals participating in a colon polyps trial, after 18 months of therapy. Furthermore, in April 2005 the FDA ordered Pfizer to withdraw its COX-2 inhibitor, Bextra®. Although the FDA permitted Pfizer to continue marketing another COX-2 inhibitor, Celebrex®, it ordered Pfizer to place a 'black box' warning in the package insert addressing the fact that patients taking Celebrex® (as with Vioxx® and Bextra®) were at an increased risk of suffering from heart attacks and/or stroke. The FDA also stipulated that serious warnings must be provided for all drugs in the NSAID class. Unfortunately, at the end of the day, it is the patient who is the real victim in this state of affairs. A storm cloud has definitely formed over RA therapy because, notwithstanding other effective classes of RA medications, it is the chronic, relentless and seemingly unremitting pain with its attendant disability that negatively impacts the quality of life of victims suffering from this disease. With this in mind, The American College of Rheumatology (ACR) has voiced its concern to the FDA advisory board regarding their decision that black box warnings should be placed in package inserts for over-the-counter (OTC) and non-selective NSAIDs. The ACR is enthusiastic about collaborating with the FDA to give healthcare providers accurate information about these drugs, hopefully

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alleviating patients' and physicians' anxieties. I agree with the ACR. In a recent letter to the FDA, the ACR stated that the FDA 'faced difficult challenges in assuring the efficacy and safety of an increasing number of medications while supplying the public and healthcare providers with accurate information regarding these RA therapies'. In a recent survey of 500 RA patients, taken by the ACR, it was shown that '100 percent of respondents would be interested in new treatments for RA that relieve pain more-completely or provide longer periods of relief from pain'. Indeed, the FDA must always take measures to insure the efficacy and safety of every medication before issuing market approval. Might it be reasonable, however, to propose that the physician and the patient are afforded more opportunities to consider the advantages and disadvantages associated with a given traditional NSAID and/or COX-2 therapy; thus deciding upon the safest and most efficacious course of action to pursue on a patient-specific basis? Many RA suffers maintain that it is 'worth the risk' to continue taking their Vioxx®, Celebrex® or Bextra® for relief from pain, inflammation and early-stage disability.

The enemy below

Disease-modifying antirheumatic drugs

Whereas traditional NSAIDs suppress the clinical manifestations of RA they do not affect the underlying disease process in the rheumatoid joint. The auto-immunological components of joint synovitis might be the engines that drive the hypertrophic, invasive and erosive synovium (pannus), degrading joint-cartilage, bone, tendons and ligaments [1]. Thus, the ectopic lymph node-like characteristics of the inflamed synovium, the site of an immune reaction (germinal centers and follicles, T cells, B cells, plasma cells, dendritic cells and macrophages) [6], are targeted by a class of immunosuppressive, immunomodulatory therapeutics that are classified as disease-modifying antirheumatic drugs (DMARDs). Methotrexate, sulfasalazine, hydrochloroquine, leflunomide and azathioprine are DMARDs that are prescribed for RA [7]. Whereas DMARDS were heretofore administered as a second-line RA therapy they have recently become a popular choice for many rheumatologists. Methotrexate is currently the first treatment option for many physicians because of its efficacy and relative safety [8]. It has been demonstrated that DMARDs suppress the clinical manifestations of RA, slow the radiographic progression of joint erosions and, on occasion, induce transient remission of the disease [8]. DMARDs are administered early, often within three months of RA diagnosis. This aggressive dosing paradigm is employed because significant joint erosion occurs within two years of disease onset [9].

Corticosteroids

Corticosteroids [glucocorticoids (GCs)] have been a blessing and a liability as therapies for RA. In truth, when administered as a low-dose and short-duration therapy, corticosteroids (e.g. prednisone) exert remarkable anti-inflammatory effects, suppressing the clinical signs, symptoms and early-stage disability of RA [10]. Definitive data have also shown these drugs display DMARD-like activity in retarding the progression of joint erosions [11]. However, their broad spectrum of side effects and attendant morbidity preclude their use by many rheumatologists; other physicians prescribe corticosteroids on a patient-selective basis or they entirely shun them.

GCs have been a significant clinical benefit to many RA patients. However, to maintain these effective drugs in the RA therapeutic armamentarium, breakthrough studies are being focused on the development of new and novel GC-like agents with benefit-safety profiles superior to those of currently used GCs. Strategies aimed at pharmacologically dissociating the anti-inflammatory component from the side-effect moiety of the standard GC molecular structure led to the discovery of selective GC receptor agonists (SEGRAs) [12]. These compounds, in addition to the discovery of new GC receptor ligands [13,14] and together with enhanced insight into the molecular mechanism(s) of action of GCs as they relate to efficacy and safety [15], bode well for the future of RA drug discovery.

Biologics

The autoimmune response that initiates and sustains the pathogenesis of RA is orchestrated by a network of proteins termed cytokines [16]. Two prominent members of the cytokine family, interleukin (IL)-1 and tumor necrosis factor (TNF)-α, are produced by cells in the rheumatoid joint [17] and mediate a lot of the structural joint damage in RA [16,17]. Preclinical efforts specifically focused on these two cytokines gave rise to DMARD-like RA therapies, known as biological response modifiers (BRMs): Etanercept (Enbrel®, Immunex and Wyeth) is a recombinant human TNF receptor 2 (TNFR2)-Fc fusion protein, whereas infliximab (Remicade®, Centocor) is a mouse–human chimeric anti-TNF-α monoclonal antibody (mAb) and adalimumab (Humira®, Abbott Laboratories) is a completely human anti-TNF-α mAb. All three BRMs form a complex with TNF-α, thus inactivating it [18]. Anakinra (Kineret®, Amgen) is a recombinant human IL-1 receptor antagonist (IL-1Ra) that competitively inhibits IL-1 binding to the type 1 IL-1 receptor (IL-1R1) [19,20]. Currently, BRMs are prescribed for RA patients who are unresponsive to DMARD therapy and/or not completely responsive to methotrexate. These biologics have a quicker onset of action than DMARDs and all three anti-TNF-α and the anti-IL-1 medications suppress the clinical manifestations of RA, improve patient mobility and retard the radiographic progression of joint erosions [20–24]. As seen with traditional DMARDs, BRMs appear to be most efficacious when treatment is initiated shortly after disease onset. The clinical efficacy of these target-specific biologics signifies the prominent role(s) played by TNF-α and IL-1 in the pathogenesis of RA. Unfortunately, parental administration, healthcare coverage and the high medical costs associated with BRMs restrict their use and deprive certain RA patients of this efficacious therapy. TNF-α is a mediator of host defense mechanisms and IL-1 also has physiological functions. Thus, BRMs are contraindicated in RA patients with infections and should be used judiciously in individuals susceptible to infection. Accordingly, these biologics continue to receive postmarketing surveillance.

Two new biologics were recently shown to have potential use in the treatment of RA. IL-6 is a pleiotropic cytokine (produced by cells in the inflammatory synovial infiltrate) that contributes to joint destruction in RA [25]. Thus, IL-6 is another target for therapeutic intervention in RA. A humanized anti-IL-6

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receptor mAb (atlizumab, MRA), which selectively inhibits IL-6, was reported to reduce the signs and symptoms as well as suppress disease activity in a multicenter clinical trial with 164 RA patients [26]. Another biologic, rituximab (Rituxan®, IDEC-C2B8, Roche and Genentech and Biogen), is a chimeric, mouse anti-human-CD20 mAb that is used as a B cell depleting therapy in neoplastic diseases [27]. In a recent Phase IIb clinical study, a combination of rituximab and methotrexate was found to be better than methotrexate monotherapy in reducing the signs and symptoms of RA [28]. It is clear that RA is not a one-mediator cell or tissue disease with a one drug solution. Hence, the judicious use of combination therapy might be a crucial way to increase clinical efficacy.

Traditional DMARD monotherapy is not always effective in controlling joint disease. Therefore, clinical trials were undertaken with DMARD combination therapy in patients with early-stage RA. Significantly, more patients on triple combination therapy (methotrexate, sulfasalazine and hydrochloroquine) experienced a greater suppression of the signs and symptoms of RA than those on double combination therapy and double combination therapy was more efficacious than monotherapy [29–31]. Triple and double combination therapy is also superior to monotherapy in retarding the radiographic progression of joint erosions and inducing remission in RA patients [29]. Increased toxicity was not observed with either triple or double DMARD combination therapy, in contrast to monotherapy. Studies of this kind portend, in part, the future of RA therapy because if the safety of combination therapy is maintained these DMARDs, with their respective mechanisms of action, could act synergistically, affording greater pain relief and slowing disease activity by targeting more components of the autoimmune process in arthritic joints than monotherapies can target. Hence, further consideration is being given to diversify combinatorial DMARD and BRM therapy in early-stage RA.

Although IL-1 and TNF-α stimulate each other's production and, thus, appear to be an attractive combination treatment, at this time BRM combination therapy (e.g. etanercept and anakinra) is not a recommended treatment for RA [32]. However, etanercept, adalimumab, infliximab or anakinra in combination with methotrexate are very effective in suppressing the clinical manifestations of RA and in retarding the progression of joint erosions [20–24].

The promise of tomorrow

T cells are major players in the pathogenesis of RA [2] requiring two signals for full activation. The first signal entails the interaction between the T cell receptor (TCR), expressed on arthritogen-specific naïve T cells, and a pathogen-derived autoantigen, presented by antigen-presenting cells (APC) in the context of MHC. The second signal is generated upon the interaction of two co-stimulatory molecules, T cell-associated CD28 and APC-associated CD80 (B7-1) and/or CD86 (B7-2). Fully activated T cells mediate the autoimmune response in RA. Cytotoxic lymphocyte-associated antigen-4 (CTLA-4) surface expression on T cells is increased after their activation and, by competing with CD28 binding to B-7, CTLA-4 downregulates T cell activation and inhibits T cell proliferation [2]. CTLA4-IgG_1 (abatacept), a fusion protein, and its more-potent variant, LEA29Y (a mAb), suppressed the clinical signs and symptoms of RA and slowed the radiographic progression of joint erosions in two Phase III clinical trials with RA patients [33,34]. As with other BRMs, these promising biologics specifically target a seminal component of the autoimmune process in RA.

Bisphosphonates (BPs) are efficacious anti-resorptive drugs that increase bone mineral density (BMD) and decrease the incidence of osteoporosis-related fractures; therefore becoming a favorable treatment for bone diseases [35]. Given the marked bone erosions and structural damage observed in the rheumatoid joint, BPs are a surprisingly ineffective treatment for RA therapy. Recently, however, zoledronate (a newer BP approved for the treatment of osteoporosis and bone metastases in cancer patients) significantly and safely retarded the progression of bone erosions in the RA wrist or hand [36]. This intravenously administered BP also slowed the emergence of new erosions and increased BMD in the affected joints [36]. When administered as a monotherapy or in combination with an NSAID, a DMARD or a BRM, zoledronate appears to merit further consideration as a RA therapy.

Gene therapy has received a lot of attention as an experimental therapy for several clinical disorders [37]. Indeed, numerous preclinical studies have demonstrated the suppressive effects of several genes in animal-model simulations of RA and osteoarthritis [38,39]. However, a major concern with gene therapy in humans is the specific vector used as the carrier of the gene encoding the therapeutic molecule. Unfortunately, several tragic events strongly emphasize this point [40]. A proof-of-concept clinical study, published by Evans *et al.* [41], employed *ex vivo* gene therapy wherein autologous synovial cells were transduced with an IL-1Ra transgene-containing retrovirus and the transduced cells were injected into the diseased hand joints of RA patients one week before joint replacement. Successful gene transfer was confirmed by the expression of the IL-1Ra transgene and the synthesis of IL-1Ra protein by the excised synovium. This procedure proved to be safe and well-tolerated by RA patients [41]. Nevertheless, further clinical trials are impeded by several key issues. In this context Evans believes, 'an allograftable, genetically engineered, universal cell would bring *ex vivo* gene therapy back into play; and the appropriate non-viral vector would be ideal for *in vivo* (injection of a therapeutic gene-containing non-viral vector into rheumatoid joint synovial tissue) gene therapy'. Indeed, sustained and safe expression of a protein therapeutic delivered to the rheumatoid joint could evolve into an effective treatment for arthritis, partly because gene therapy could potentially be less frequently administered than a BRM. Notwithstanding the vector issue, RA is not a lethal disease, and BRMs have proven to be successful protein-based RA therapies. Accordingly, with a much higher incidence than RA, osteoarthritis, for which there is no superior therapy and with a resulting high occurrence of joint replacements, might be a more viable application for gene therapy. Once the vector issue is resolved, new gene therapy trials with arthritis patients should be funded and undertaken in osteoarthritis patients and patients with other orthopaedic disorders.

High-dose chemotherapy (HDC) and autologous stem cell transplantation is

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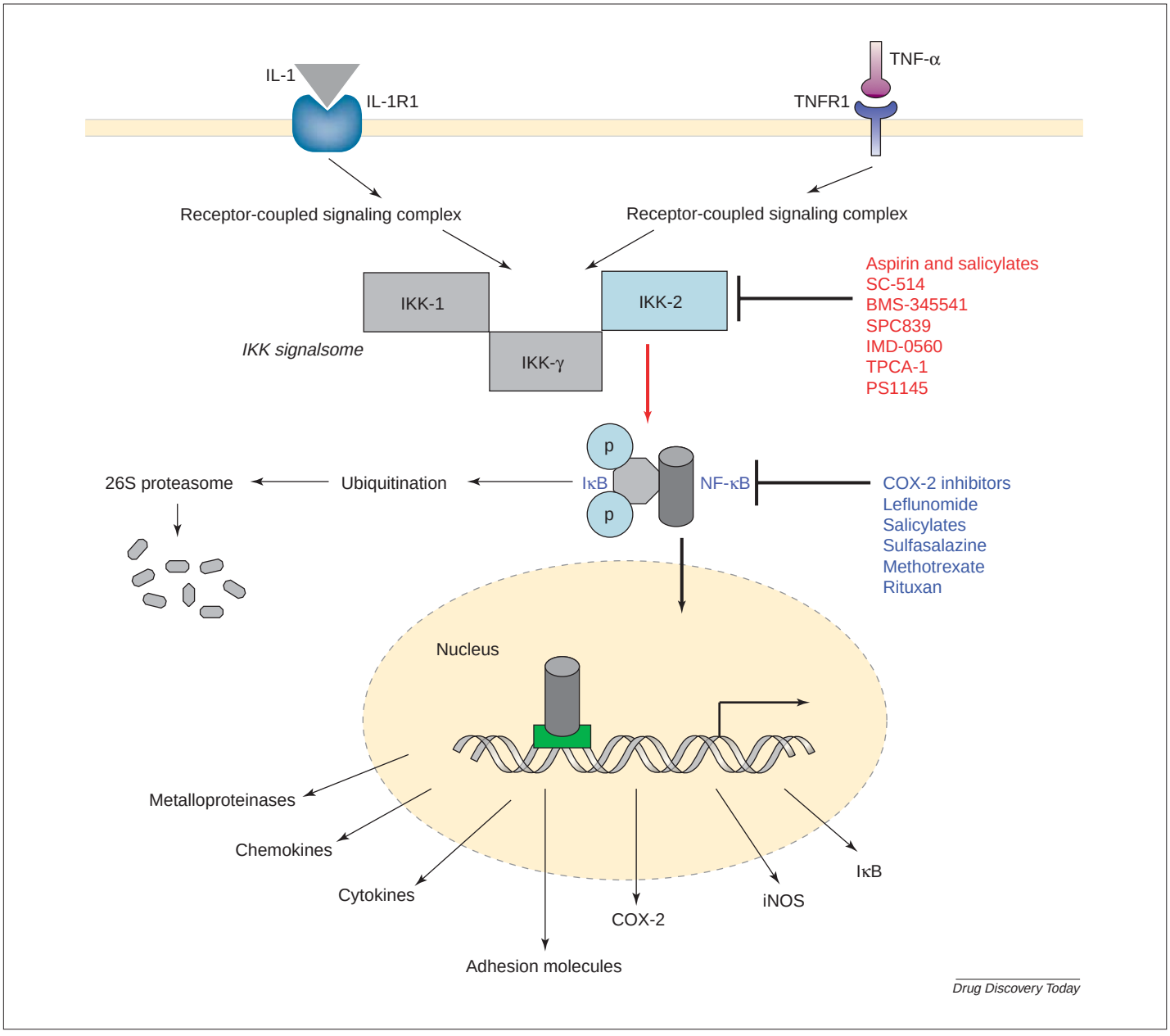

FIGURE 1

Proinflammatory gene transcription. Nuclear factor κB (NF-κB) is a prominent transcription factor in rheumatoid joint tissue that activates genes encoding a broad spectrum of proinflammatory molecules that mediate the immunopathogenesis of rheumatoid arthritis (RA). Selective and cell-specific inhibition of NF-κB could constitute a safe and efficacious therapy for RA. Abbreviation: iNOS, inducible nitric oxide synthetase.

another potentially efficacious, safe RA therapy. Like gene therapy, it has received limited clinical exposure. The concept behind this strategy suggests that the chemotherapeutic removal of autoreactive and/or potentially autoreactive T cells followed by normal or naïve T cell replacement with bone marrow-derived stem cell infusion, might negatively impact the pathogenesis of RA [42]. This therapeutic regimen reduced the clinical manifestations and disability in RA patients [43,44] and, in a follow-up analysis, slowed the rate of joint damage [45]. Patients in these studies, who were heretofore refractory to DMARD therapy, became responsive to these drugs [44]. Nevertheless, HDC-triggered immunoablation renders the patient susceptible to infection. Understandably, only a small number of RA patients have gone through this procedure Hence, only time and further study will reveal the true benefit and safety of this RA therapy in patients with severe disease, unresponsive to all other classes of therapy.

Therapeutic targets in cell signaling pathways

Gene transcription

Several efficacious RA therapies target either the cellular constituents (in the case of DMARDs) or cell-derived mediators (in the case of

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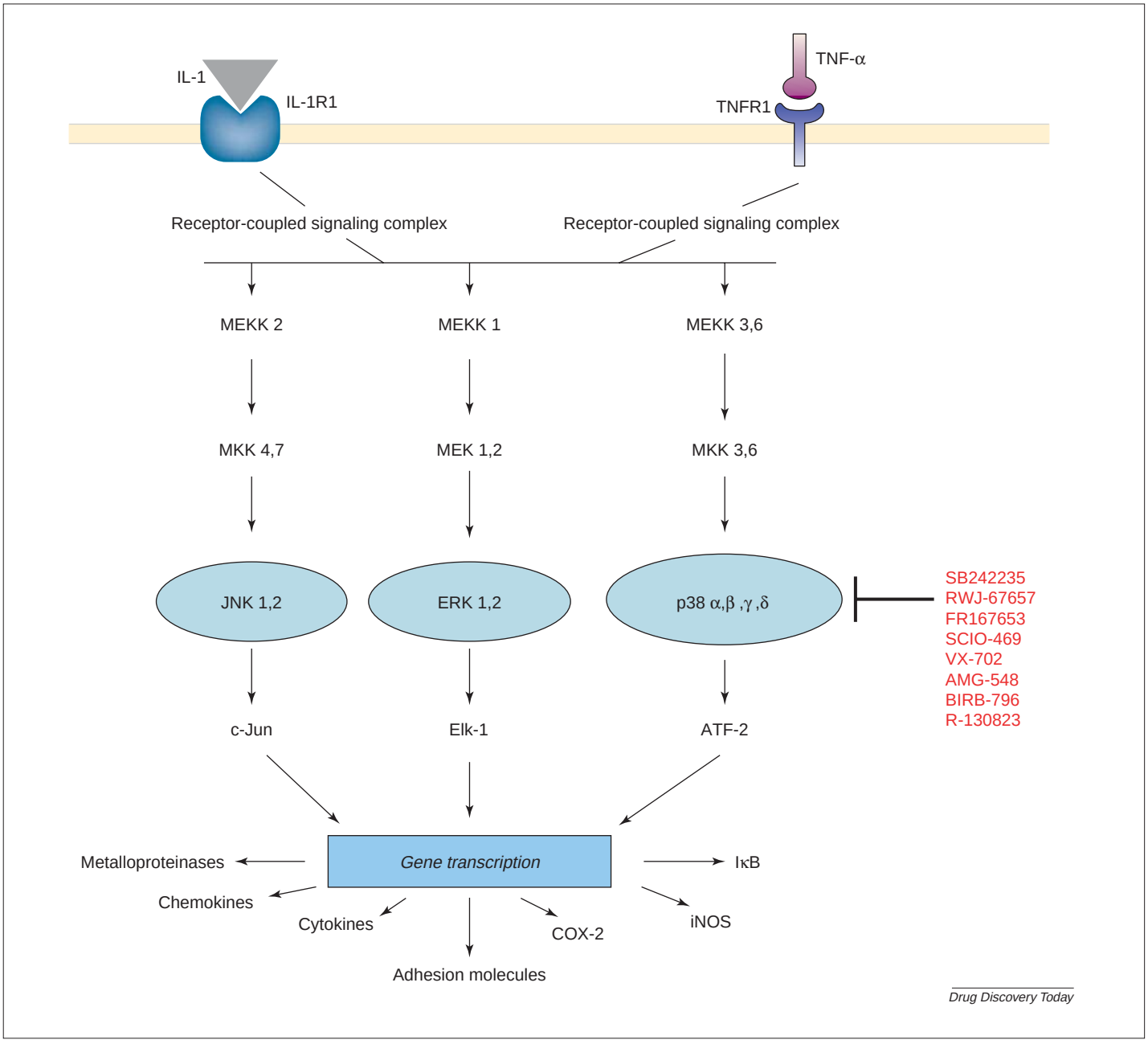

FIGURE 2

p38 kinase inhibition: a novel therapy for rheumatoid arthritis. Investigation of Interleukin (IL)-1 and tumor necrosis factor (TNF)-α receptor-coupled activation of mitogen-activated protein (MAP) kinase cascades in numerous cell types in the rheumatoid arthritic joint suggests that p38 represents a viable target for therapeutic intervention in rheumatoid arthritis. Abbreviation: iNOS, inducible nitric oxide synthetase.

biologics) of inflammatory joint disease. However, several of the seminal components of the receptor-coupled signal transduction pathways that are intimately involved in the pathogenesis of RA have become the subject of significant biomedical investigation. Nuclear factor κB (NF-κB), a ubiquitous and well-defined transcription factor, has been demonstrated to activate genes (in various inflammatory cell types) that encode a broad spectrum of proinflammatory molecules (Figure 1). Indeed, the activation of NF-κB by TNF-α and IL-1 (Figure 1), explains the interest in targeting these cytokines with several of the aforementioned biologics. However, NF-κB also transcriptionally activates genes encoding molecules involved in host defense. The cell's capacity to activate genes controlling physiological cell death (apoptosis) is driven, in part, by NF-κB [46]. Accordingly, the search for a selective inhibitor of NF-κB as a potential RA therapy is a daunting task. Although many agents are in early-stage drug discovery, several of the aforementioned, currently used therapies, as well as new mechanistically diverse RA therapies [47–53], have been reported to inhibit NF-κB activity (Figure 1). Nevertheless,

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specificity is the nemesis of the pharmacologist and we must endeavor to maximize the benefit:risk ratio of these agents. The incidence of side effects with many RA therapies could be attributed, in part, to their nonspecific effects on NF-κB and/or other transcription factors.

Protein kinases and NF-κB activation

The selective binding of inflammatory agonists, such as IL-1 and TNF-α, to their cognate receptors on numerous cell types in the inflamed synovium triggers a cascade of NF-κB-mediated events that results in a broad spectrum of cellular responses that are associated with arthritic joint disease. Careful analysis of these signaling pathways has identified an apparent point of convergence between them, which could present a viable target for therapeutic intervention. The IκB (inhibitor of NF-κB) kinase (IKK) signalsome is a cytoplasmic complex comprising two catalytic entities, IKK-1 and IKK-2, as well as IKKγ [thought to perform a scaffolding and/or signaling platform function (Figure 1)] [54–56]. Atypical of many transcription factors, in unstimulated cells NF-κB is localized in the cytoplasm and rendered inactive by complexing with IκB. In IL-1- and/or TNF-α-activated cells an upstream kinase preferentially activates IKK-2 that, in turn, phosphorylates IκB, thus programming it for destruction. The phosphorylated IκB is sequentially ubiquitinated and degraded by the 26S proteasome (Figure 1) [54–56]. The dissociation of IκB from NF-κB exposes the nuclear localization signal on NF-κB and initiates its nuclear import whereupon it binds to cognate motifs in the promoters of various genes initiating transcription (Figure 1) [54–56]. It is apparent, therefore, that the selective inhibition of IKK-2 could represent another molecular strategy for interfering with NF-κB and, thus, constitute an effective RA therapy. Significant efforts on the part of the pharmaceutical and biotech industries and academia have yielded several interesting IKK inhibitors. SC-514 (Pharmacia), BMS-345541 (Bristol-Myers Squibb), IMD-0560 (University of Tokyo), TPCA-1 (GalaxoSmithKline), PS1145 (Millennium Pharmaceuticals), SPC839 (Signal Pharmaceuticals) and aspirin and salicylate have been reported to inhibit IKK-2 activity as well as IκB phosphorylation, NF-κB nuclear transport and NF-κB transcriptional activation of genes encoding proinflammatory molecules in a broad spectrum of cell-based assays (including rheumatoid synovial fibroblasts) [57–62]. Additionally, BMS345541, SPC839, IMD-0560 and TPCA-1 suppressed the clinical score, incidence and severity of collagen-induced and adjuvant-induced polyarthritis in rodents [58–60,63]. In several cases, this correlated with *in vivo* suppression of inflammatory molecule synthesis [58,60].

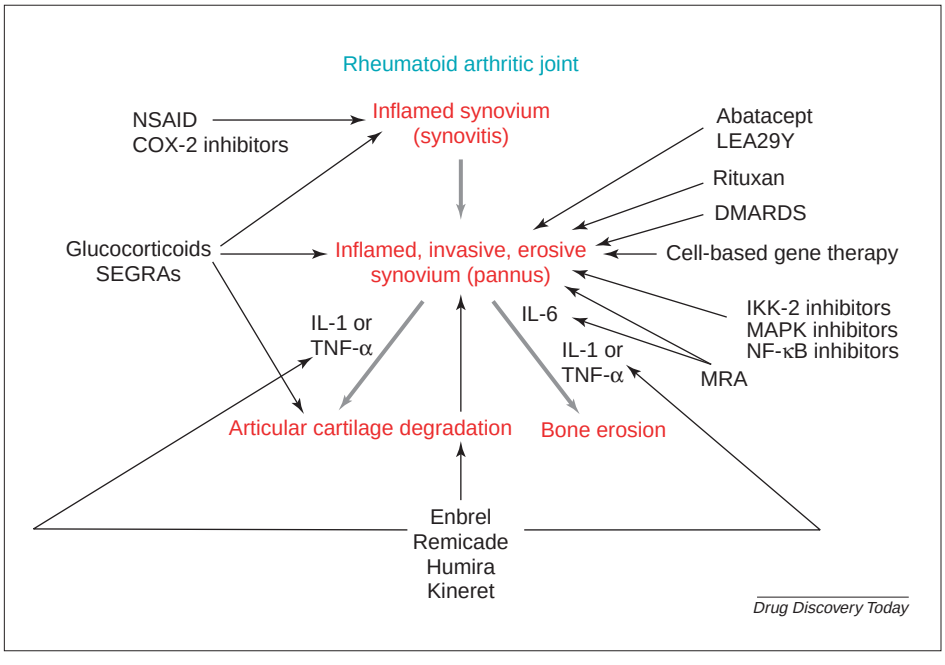

FIGURE 3

Therapeutic targets of development-stage, current and emerging treatments for rheumatoid arthritis. The pathological aspects of arthritic joint disease and their underlying components have become the targets of many therapeutic strategies focused on controlling and, hopefully, curing rheumatoid arthritis.

MAP kinases

Another component of receptor-coupled signaling pathways, stimulated by proinflammatory molecules, such as IL-1 and TNF-α, primarily comprises three mitogen-activated protein kinase (MAPK) cascades in fibroblast-like synovial cells and rheumatoid synovium (Figure 2) [64,65]. The receptor-coupled signaling complexes, organized following the agonist binding to its cognate receptor, trigger the activation of the respective downstream MAPK cascades (Figure 2) [64,65]. The sequential phosphorylation of these protein kinases leads to the phosphorylation and activation of MAPK-specific transcription factors, which, in turn, activate genes encoding inflammatory molecules (Figure 2). Extracellular signal-related kinase (ERK) is typically associated with cell survival, proliferation and differentiation. It is activated by growth factors and mitogens, whereas c-Jun N-terminal kinase (JNK) and p38 signaling is linked to inflammation and cell death, triggered by cellular stress and inflammatory cytokines. Investigation of the MAPK signaling pathways reveal that p38, in particular the α and β isoforms [66], represents a viable therapeutic target for the treatment of RA. SB-242235 (SmithKlineBeecham), RWJ-67657 (University Hospital Groningen, Netherlands), FR167653 (Osaka Graduate School of Medicine, Japan), SCIO-469 (Scois), VX-702 (Vertex), AMG-548 (Amgen), BIRB-796 (Boehringer Ingelheim) and R-130823 (Sankyo Co) are potent inhibitors of p38 activity (Figure 2) and several of these agents suppress inflammatory mediator production [IL-1, TNF-α, IL-6, IL-8, COX-2 and metalloproteinases (MMP)] in cell-based models [67–72] and arthritis in rodent models [69,71,73]. AMG-548 is in Phase I, SCIO-469 is in Phase IIb, VX-702 is in Phase II and BIRB-796 is currently in Phase IIb and Phase II clinical trials in RA patients [70,71,74,75]. The therapeutic outcome of these studies will be very informative and could govern the future of p38 inhibition as an effective RA therapy.

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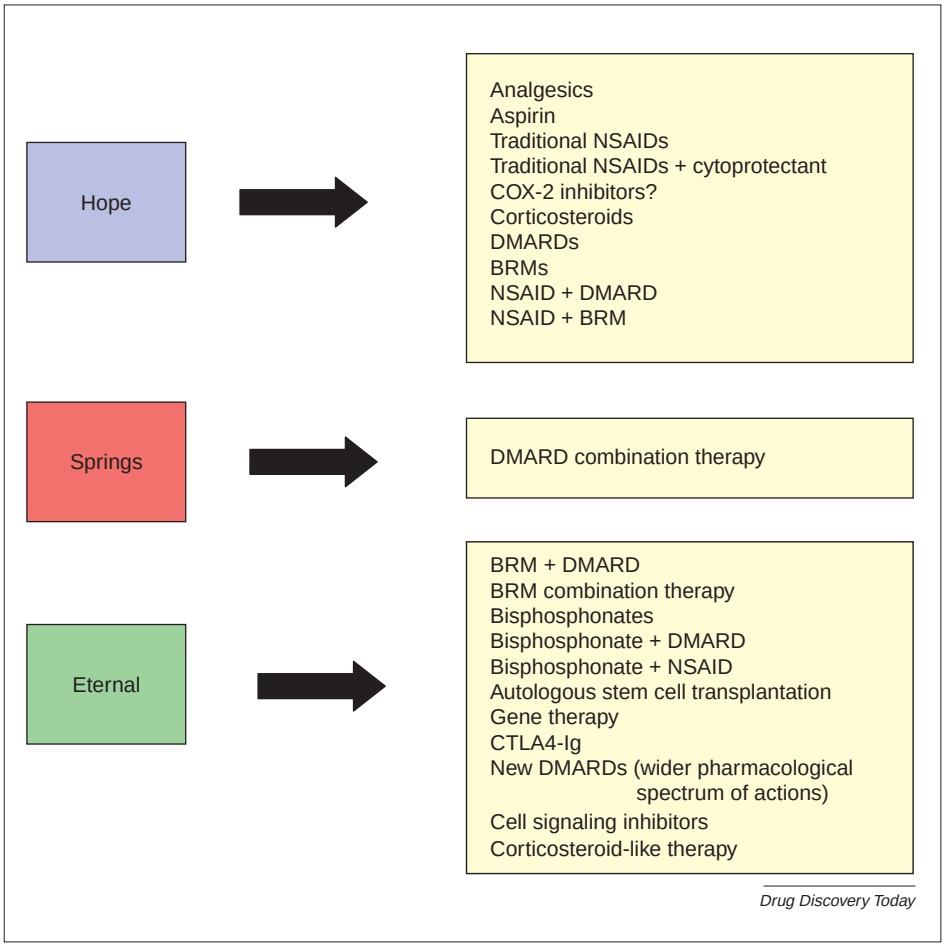

FIGURE 4

The current and potential therapeutic armamentarium for rheumatoid arthritis. Hope: the continued belief of rheumatoid arthritic patients that current therapies will ease their suffering and improve their quality of life. Springs: the clinical success achieved with early and aggressive use of disease-modifying antirheumatic drug (DMARD) combination therapy is bringing new enthusiasm into the lives of those arthritic sufferers who need more-efficacious therapies for disease management. Eternal: the sustained efforts of biomedical investigators will continue to identify new targets, which will lead to novel efficacious and, hopefully, low risk therapeutic intervention in rheumatoid arthritis.

The JNK kinase-module targets the transcription factor c-Jun for activation (Figure 2) and c-Jun homodimerizes or heterodimerizes with another transcription factor, c-Fos, to form the transcription factor AP-1. AP-1 binds to its cognate motif on the promoters of certain genes and initiates transcription. A selective JNK inhibitor, SP600125 (Celgene), suppressed IL-1-triggered c-Jun transcription, AP-1 binding to DNA and tissue-degrading MMP production in human synoviocytes as well as mitigated inflammation and joint pathology in a rodent model of arthritis [76]. We await the emergence of a selective, safe JNK inhibitor with the appropriate benefit:safety ratio required for clinical evaluation.

Of interest, p38 and JNK target activating transcription factor (ATF)-2 and c-Jun, respectively, and both MAPKs mediate the production of MMPs [70,76]. Additionally, p38 is also associated with NF-κB-mediated gene transcription [77,78]. It is known that eukaryotic genes are most often regulated by the simultaneous and synergistic actions of multiple transcription factors and this reality could become a seminal issue when undertaking a therapeutic strategy that targets immunoinflammatory mediator production.

Conclusion

The medical needs of RA patients remain unmet and no current therapy constitutes a cure for this chronic autoimmune disease. Notwithstanding the systemic components of RA, the pathogenesis of this disorder, for unknown reasons, resides in joint tissue. The seminal, pathological constituents of RA include an inflamed synovial membrane that, in a matter of months, will develop into an inflamed, invasive and erosive tumor-like tissue mass that degrades bone and articular cartilage in the affected joints (Figure 3). Accordingly, these pathological aspects of arthritic joint disease and their underlying components have become the targets of many therapeutic strategies focused on controlling and, hopefully, curing RA. As discussed herein, NSAIDs are mainstay RA therapies that, in most cases, offer symptomatic relief to arthritis sufferers (Figure 3). The emergence of COX-2 inhibitors offered hope and optimism to patients and physicians but the surprising and untoward liabilities associated with these drugs have triggered significant consternation and frustration in the medical community and the FDA. A resolution and refocused perspective to this sensitive issue would bring clinical relief, peace of mind and hope to the RA patient. The discovery and early development of SEGRAs as replacement GC therapy could, in time, offer the RA patient a treatment with the efficacy of GCs but without the side effects that frequently accompany the use of these drugs (Figure 3). Increasingly, physicians are administering established DMARDs (methotrexate, sulfasalazine, hydrochloroquine, leflunomide and azathioprine) earlier in the disease process and insightful DMARD combination therapy is reducing the progression of joint destruction in RA on a more frequent basis. In fact, several DMARDs target the cellular components (T and B lymphocytes) of the inflamed synovium (Figure 3). Biologics, such as Humira, Enbrel, Remicade and Anakinra, that target specific proinflammatory cytokines (IL-1 and TNF-α) and their cytokine receptors (IL-1 and TNF-α stimulate immune and inflammatory mediator production by rheumatoid synovial cells, and are themselves produced by these cells) have established efficacy in controlling joint erosions. In combination with methotrexate, these BRMs are being considered for early use and certainly in those

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patients resistant to DMARD therapy (Figure 3). Increased understanding of the disease process has given us emerging RA therapies, such as cell–cell (e.g. T cell and APC) co-stimulation inhibitors (abatacept and LEA29Y), anticytokine therapy (MRA) and a B cell depletor (rituxan) (Figure 3). These new biologics are currently in clinical trials for RA. New therapeutic perspectives, such as gene therapy and stem cell transplantation, applied to other autoimmune diseases could, in time, afford promising alternatives to selected RA patients. Investigation of signal transduction pathways and their role in mediating the production of a broad spectrum of immune and inflammatory mediators, by the inflamed synovium and other joint tissue, has led to the discovery of novel and potentially selective molecular therapies that target inflammatory gene transcription (NF-κB and IKK-2 inhibitors) and MAPK signaling pathways (p38 inhibitors) (Figure 3). These antagonists of signal transduction have demonstrated their target-based inhibitory effect in pathologically germane cell-based systems and they suppress the arthritic process in animal models. Moreover, several of these molecules are in clinical trials with RA patients.

At the end of the day, I respectfully submit that the RA patient has reason for optimism regarding current and future RA therapies. NSAIDs and analgesics are efficacious therapies and DMARDs and BRMs offer hope, if not the expectation, for significant relief from pain, disability and joint disease. Nevertheless, in response to another question posed to RA patients in the aforementioned 500 patient survey, 'nearly three-quarters of people taking either DMARDs or BRMs are very, or extremely, interested in having their treating physician tell them about new RA therapies'. Certainly, patient heterogeneity, in the context of variable drug responses or unresponsiveness, contributed to this answer. Nevertheless, as our knowledge of the pathological components of autoimmune inflammatory joint disease and comfort with and understanding of RA therapies continues to increase, we will continue to witness the emergence of more-efficacious biologic and DMARD therapies, as well as the birth of mechanistically new, novel, effective and safe RA therapies (Figure 4). May hope spring eternal!

References

1 Firestein, G.S. (2001) Etiology and pathogenesis of rheumatoid arthritis. In *Kelley's Textbook of Rheumatology* (Ruddy, S. *et al*., eds), pp.921–966, W.B. Saunders Company
2 Kavanaugh, A.F. and Lipsky, P.E. (1999) Rheumatoid Arthritis. In *Inflammation- Basic Principles and Clinical Correlates* (Gallin, J.I. and Snyderman, R., eds), pp. 1017–1037, Lippincott Williams and Wilkins
3 Rostom, A. *et al*. (2000) *Cochrane Database Syst. Rev*. CDOO2296
4 Bocanegra, T.S. *et al*. (1998) Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial. Arthrotec osteoarthritis study group. *J. Rheumatol.* 25, 1602–1611
5 Goldstein, J.L. *et al*. (2001) Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. *Am. J. Gastroenterol*. 96, 1019–1027
6 Weyand, C.M. and Goronzy, J.J. (2003) Ectopic germinal center formation in rheumatoid synovitis. *Ann. N. Y. Acad. Sci.* 987, 140–149
7 Cronstein, B.N. (1999) Second-line antirheumatic drugs. In *Inflammation- Basic Principles and Clinical Correlates* (Gallin, J.I. and Snyderman, R., eds), pp. 1227–1237, Lippincott Williams and Wilkins
8 Kwoh, C.K. *et al*. (2002) Guidelines for the management of rheumatoid arthritis: 2002 update – American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines *Arth. Rheum*. 46, 328–346
9 Pincus, T. *et al*. (1998) Early radiographic joint space narrowing and erosion and later malalignment in rheumatoid arthritis; a longitudinal study. *J. Rheumatol.* 25, 636–640
10 Stein, C.M. and Pincus, T. (2001) Glucocorticoids. *In Kelley's Textbook of Rheumatology* (Ruddy, S. *et al*., eds), pp. 823–840, W.B. Saunders Company
11 Bijlsma, J.W.J. *et al*. (2002) Glucocorticoids in rheumatoid arthritis: effects on erosions and bone. *Ann. N. Y. Acad. Sci.* 966, 82–90
12 Schacke, H. *et al*. (2002) SEGRAs: a novel class of anti-inflammatory compounds. *Ernst Schering Res. Found. Workshop* 40, 357–371
13 Buttgereit, F. *et al*. (2005) Current insights into the development of new glucocorticoid receptor ligands. *Z. Rheumatol*. 64, 170–176
14 Song, I.H. *et al*. (2005) New glucocorticoids on the horizon: repress, don't activate! *J. Rheumatol.* 32, 1199–1207
15 Schacke, H. *et al*. (2005) Dissociated glucocorticoid receptor ligands: compounds with an improved therapeutic index. *Curr. Opin. Investig. Drugs* 6, 503–507
16 Choy, E.H.S. and Panayi, G.S. (2001) Cytokine pathways and joint inflammation in rheumatoid arthritis. *N. Engl. J. Med*. 344, 907–916
17 Feldman, M. *et al*. (1996) Role of cytokines in rheumatoid arthritis. *Annu. Rev. Immunol*. 14, 397–440
18 Calabrese, L.H. (2003) Molecular differences in anticytokine therapies. *Clin. Exp. Rheumatol*. 21, 241–248
19 Smith, R.J. *et al*. (1991) Biologic effects of an interleukin-1 receptor antagonist protein on interleukin-1-stimulated cartilage erosion and chondrocyte responsiveness. *Arthritis Rheum*. 34, 78–83
20 Arend, W.P. *et al*. (1998) Interleukin-1 receptor antagonist: role in biology. *Annu. Rev. Immunol*. 16, 27–55
21 Genovese, M.C. *et al*. (2002) Etanercept versus methotrexate in patients with early rheumatoid arthritis: two year radiographic and clinical outcomes. *Arthritis Rheum*. 46, 1443–1450
22 Bresnihan, B. (2002) Preventing joint damage as the best measure of biologic drug therapy. *J. Rheumatol. Suppl*. 65, 39–43
23 Keystone, E.C. *et al*. (2004) Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum*. 50, 1400–1411
24 Lorenz, H.M. and Kalden, J.R. (2002) Perspectives for TNF-alpha-targeting therapies. *Arthritis Res*. 4(Suppl 3), S17–S24
25 Nishimoto, N. *et al*. (2004) Treatment of rheumatoid arthritis with humanized anti-interleukin 6 receptor antibody. *Arthritis Rheum*. 50, 1761–1769
26 Yokota, S. *et al*. (2005) Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathetic arthritis. *Arthritis Rheum*. 52, 818–825
27 Czuczman, M.S. *et al*. (2002) Rituximab I combination with CHOP or fludarabine in low-grade lymphoma. *Semin. Oncol*. 29, 36–40
28 Edwards, J. *et al*. (2004) Efficacy of B-cell target therapy with rituximab in patients with rheumatoid arthritis. *N. Engl. J. Med.* 350, 2572–2581
29 Calguneri, M. *et al*. (1999) Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin. Exp. Rheumatol*. 17, 699–704
30 Mottonen, T. *et al*. (1999) Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomized trial. *Lancet* 353, 1568–1573
31 O'Dell, J.R. *et al*. (2002) Treatment of rheumatoid arthritis with methotrexate and hydrochloroquine, and methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 46, 1164–1170
32 Genovese, M.C. *et al*. (2004) Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum*. 50, 1412–1419
33 Ruderman, E.M. and Pope, R.M. (2005) The evolving clinical profile of abatacept (CTLA4-Ig): a novel co-stimulatory modulator for the treatment of rheumatoid arthritis. *Arthritis Res. Ther*. 7(Suppl. 2), S21–S25
34 Kremer, J.M. *et al*. (2005) Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase IIb double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 52, 2263–2271
35 Dunn, C.J. and Goa, K.L. (2001) Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs* 61, 685–712
36 Jarrett, S. *et al*. (2004) First evidence of structural benefit from a bisphosphonate, zoledronic acid, in rheumatoid arthritis. *EULAR* 2004, 9–12 June 2004, Berlin, Germany (Abstract 0P0002)
37 Chuah, M. (2005) Challenges in advancing the field of gene therapy – American Society of Gene Therapy Stockholders Meeting. A critical review of the science,

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medicine and regulation. *IDrugs* 8, 483–486
38 Evans, C.H. *et al*. (1999) Gene therapy for rheumatic diseases. *Arthritis Rheum*. 42, 1–16
39 Pan, R.Y. *et al*. (2000) Therapy and prevention of arthritis by recombinant adeno-associated virus vector with delivery of interleukin-1 receptor antagonist. *Arthritis Rheum*. 43, 289–297
40 Dettweiler, U. and Simon, P. (2001) Points to consider for ethics committees in human gene therapy trials. *Bioethics* 15, 491–500
41 Evans, C.H. *et al*. (2005) Gene transfer to human joints: progress toward a gene therapy for arthritis. *Proc. Natl. Acad. Sci. U. S. A*. 102, 8698–8703
42 Verburg, R.J. *et al*. (2002) High dose chemotherapy and autologous hematopoietic stem cell transplantation for rheumatoid arthritis. *Hum. Immunol*. 63, 627–637
43 Verburg, R.J. *et al*. (2001) High dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with rheumatoid arthritis: results of an open study to assess feasibility, safety, and efficacy. *Arthritis Rheum*. 44, 754–760
44 Snowden, J.A. *et al*. (2004) Autologous hemopoietic stem cell transplantation in severe rheumatoid arthritis: a report form the EMBT and ABMRT. *J. Rheumatol.* 31, 482–488
45 Verburg, R.J. *et al*. (2005) Reduction of joint damage in severe rheumatoid arthritis by high-dose chemotherapy and autologous stem cell transplantation. *Arthritis Rheum*. 52, 421–424
46 Ghosh, S. and Karin, M. (2002) Missing pieces in the NF-κB puzzle. *Cell* 109, S81–S96
47 Vega, M.I. *et al*. (2005) Rituximab-induced inhibition of YY1 and BCL-x_L expression in ramos non-hodgkin's lymphoma cell line via inhibition of NF-κB activity: role of YY1 and BCL-x_L in fas resistance and chemoresistance, respectively. *J. Immunol*. 175, 2174–2183
48 Manna, S.K. *et al*. (2000) Leflunomide suppresses TNF-induced cellular responses: effects on NF-κB, activator protein-1, c-Jun N-terminal kinase, and apoptosis. *J. Immunol.* 165, 5962–5969
49 Majumdar, S. and Aggarawal, J. (2001) Methotrexate suppresses NF-κB activation through inhibition of IκBa phosphorylation and degradation. *J. Immunol.* 167, 2911–2920
50 Shishodia, S. *et al*. (2004) Cycloxygenase (COX)-2 inhibitor Celecoxib abrogates TNF-induced NF-κB activation through inhibition of IκBα kinase and Akt in human non-small cell lung carcinoma: correlation with suppression of COX-2 synthesis. *J. Immunol.* 173, 2011–2022
51 Meng, X.W. *et al*. (1997) Induction of apoptosis in peripheral blood lymphocytes following treatment in vitro with hydroxychloroquine. *Arthritis Rheum*. 40, 927–935
52 Kopp, E. and Ghosh, S. (1994) Inhibition of NF-kappa B by sodium salicylate and aspirin. *Science* 265, 956–959
53 Reed, J.C. and Pellecchia, M. (2005) Apoptosis-based therapies for hematologic malignancies. *Blood* 106, 408–418
54 Mercurio, F. and Manning, A.M. (1999) Multiple signals converging on NF-κB. *Curr. Opin. Cell Biol*. 11, 226–232
55 Karin, M. and Ben-Neriah, Y. (2000) Phosphorylation meets ubiquitination: the control of NF-κB activity. *Annu. Rev. Immunol.* 18, 621–623
56 Karin, M. (1999) How NF-κB is activated. The role of the IκB kinase (IKK). *Oncogene* 18, 6867–6874
57 Kishore, N. *et al*. (2003) A selective IKK-2 inhibitor blocks NF-κB dependent gene expression in Interleukin-1β-stimulated synovial fibroblasts. *J. Biol. Chem*. 278, 32861–32871
58 McIntyre, K.W. *et al*. (2003) A selective inhibitor of IκB kinase, BMS-345541, blocks both joint inflammation and destruction in collagen-induced arthritis in mice. *Arthritis Rheum*. 48, 2652–2659
59 Okazaki, Y. *et al*. (2005) Effect of Nuclear Factor-κB inhibition on rheumatoid fibroblast-like synoviocytes and collagen-induced arthritis. *J. Rheumatol*. 32, 1440–1447
60 Podolin, P.L. *et al*. (2005) Attenuation of murine collagen-induced arthritis by a novel, potent, selective small molecule inhibitor of IκB kinase 2, TPCA-1 (2-[(aminocarbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide), occurs via reduction of proinflammatory cytokines and antigen-induced T cell proliferation. *J. Pharmacol. Exp. Ther*. 312, 373–381
61 Hideshima, T. *et al*. (2002) NF-kappa B as a therapeutic target for multiple myeloma. *J. Biol. Chem*. 277, 16639–16647
62 Yin, M.J. *et al*. (1998) The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. *Nature* 396, 77–80
63 Hammaker, D. *et al*. (2003) Signal transduction networks in rheumatoid arthritis. *Ann. Rheum. Dis.* 62(Suppl II), ii86–ii89
64 Firestein, G.S. and Manning, A.M. (1999) Signal transduction and transcription factors in rheumatic disease. *Arth. Rheum*. 42, 609–621
65 Pearson, G. *et al*. (2001) Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. *Endocr. Rev*. 22, 153–183
66 Fearns, C. *et al*. (2000) Coordinate activation of endogenous p38α, β, γ, and δ by inflammatory stimuli. *J. Leuk. Biol*. 67, 705–711
67 Badger, A.M. *et al*. (2000) Differential effects of SB-242235, a selective p38 mitogen-activated protein kinase inhibitor, on IL-1 treated bovine and human cartilage/chondrocyte cultures. *Osteoarthritis Cartilage* 8, 434–443
68 Westra, J. *et al*. (2004) Effects of RWJ-67657, a p38 mitogen activated protein kinase (MAPK) inhibitor, on the production of inflammatory mediators by rheumatoid synovial fibroblasts. *Ann. Rheum. Dis*. 63, 1453–1459
69 Wei, Y.H. *et al*. (2004) Effects and mechanisms of FR167653, a dual inhibitor of interleukin-1 and tumor necrosis factor, on adjunvant arthritis in rats. *Int. Immunopharmacol*. 4, 1625–1632
70 Dominguez, C. *et al*. (2005) p38 kinase inhibitors: many are made but few are chosen. *Curr. Opin. Drug Discov. Devel.* 8, 421–430
71 Kuma, Y. *et al*. (2005) BIRB 796 inhibits all p38 isoforms in vitro and in vivo. *J. Biol. Chem*. 280, 19472–19479
72 Wada, Y. *et al*. (2005) Novel p38 MAP kinase inhibitor R-130823 suppresses IL-6, IL-8 and MMP-13 production on spheroid culture of human synovial sarcoma cell line SW 982. *Immunol. Lett.* 101, 50–59
73 Wada, Y. *et al*. (2005) R-130823, a novel inhibitor of p38 MAPK, ameliorates hyperalgesia and swelling in arthritis models. *Eur. J. Pharmacol*. 506, 285–295
74 Dominguez, C. *et al*. (2005) p38 kinase inhibitors: many are made but few are chosen. *Curr. Opin. Drug Discov. Devel.* 8, 421–430
75 Nikas, S.N. and Drosos, A.A. (2004) SCIO-469 Scios Inc. *Curr. Opin. Investig. Drugs* 5, 1205–1212
76 Han, Z. *et al*. (2001) c-Jun N-terminal kinase is required for metalloproteinase expression and joint destruction in inflammatory arthritis. *J. Clin. Invest.* 108, 73–81
77 Saklatvala, J. *et al*. (2003) Control of the expression of inflammatory response genes. *Biochem. Soc. Symp*. 70, 95–106
78 Saccani, S. *et al*. (2002) p38-dependent marking of inflammatory genes for increased NF-kappa B recruitment. *Nat. Immunol.* 3, 69–75

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